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2. That I am well acquainted with the French and English languages;

3. That the attached is a true translation into the English language of the certified copy of French Patent Application No. 0401690 filed 20 February 2004;

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

Declared this 15th day of June 2006

V. I. Coulson.

V.I. COULSON

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PA1

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1 NAME AND ADDRESS OF THE APPLICANT OR OF THE AUTHORISED AGENT TO WHOM CORRESPONDENCE MUST BE ADDRESSED
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3 TITLE OF THE INVENTION (maximum 200 characters or spaces)
New azabicyclic compounds, a process for their preparation and pharmaceutical compositions containing them

4 DECLARATION OF PRIORITY OR REQUEST FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION
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5 APPLICANT (Mark one of the 2 boxes) ☒ **Legal person** ☐ **Natural person**

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The Applicants and the inventors are the same		☐ Yes ☒ No : **In this case, complete the "Declaration of Inventorship" form**
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François RIVIERE, Patent Engineer

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The present invention relates to new azabicyclic compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the present invention are of particular interest from a pharmacological point of view for their interaction with the central histaminergic systems *in vivo*, and may be used in the treatment of neuropathologies associated with cerebral ageing, mood disorders, eating behaviour disorders and sleep/wake cycle disturbances, as well as attention deficit hyperactivity syndrome.

Ageing of the population as a result of the increase in life expectancy at birth has in parallel brought about a substantial increase in the incidence of neuropathologies associated with age, and especially Alzheimer's disease. The principal clinical manifestations of cerebral ageing and especially neuropathologies associated with age are mnesic and cognitive function deficiencies, which may lead to dementia.

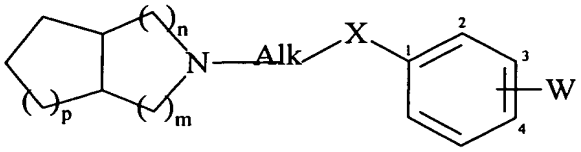
In respect of the central nervous system, recent neuropharmacological studies have demonstrated that histamine, *via* the central histaminergic systems, plays the role of a neurotransmitter or neuromodulator in physiological or pathophysiological settings (Pell and Green, *Annu. Rev. Neurosci.*, 1986, 9, 209-254; Schwartz *et al.*, *Physiol. Rev.*, 1991, 71, 1-51). Thus, it has been demonstrated that histamine plays a part in various physiological and behavioural processes such as thermoregulation, neuroendocrine regulation, circadian rhythm, cataleptic states, motor function, aggressiveness, eating behaviour, learning and memory function, and also synaptic plasticity (Hass *et al.*, *Histaminergic neurones : morphology and function*, Boca Raton, FL : CRC Press, 1991, pp. 196-208 ; Brown *et al.*, *Prog. Neurobiology*, 2001, 63, 637-672).

Studies carried out in animals have demonstrated that an increase in endogenous extra-synaptic levels of histamine enables the promotion of states of alertness, the promotion of learning and memory processes and the regulation of food intake and enables convulsive attacks to be countered. (Brown *et al.*, *Prog. Neurobiol.*, 2000, 63, 637-672; Passani *et al.*, *Neurosci. Biobehav. Rev.*, 2000, 24, 107-113). As a result, potential therapeutic indications for compounds capable of increasing the turnover or release of histamine centrally are the

treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases, such as Alzheimer's disease, Pick's disease, Korsakoff's disease and frontal lobe or sub-cortical dementias of vascular or other origins, as well as the treatment of mood disorders, convulsive attacks and attention deficit hyperactivity syndrome. Furthermore, works have shown that a histamine injection at the level of the central hypothalamic nuclei involved in the regulation of satiety reduces feeding in the rat. In addition, a hypofunctioning of histaminergic transmission has been demonstrated in genetically obese rats (Machidori *et al.*, *Brain Research*, 1992, 590, 180-186). As a result, eating behaviour disorders and obesity are likewise potential therapeutic indications for the compounds of the present invention.

A number of documents describe compounds comprising an octahydrocyclopenta-[*b*]pyrrole or octahydrocyclopenta[*c*]pyrrole moiety [US 2,962,496 ; *J. Chem. Soc., Chem. Commun.*, 1995, 10, 1009-1010 ; *Tetrahedron*, 1991, 47(28), 5161-5172 ; *Tetrahedron Lett.*, 1988, 29 (28), 3481-3482 ; *J. Med. Chem.*, 1973, 16(4), 394-397]. Some of those compounds are known for their use in the treatment of cardiovascular diseases, especially hypertension, or as a local anaesthetic, and others have been studied from the point of view of mechamism in relation to chemical reactions of the catalysed intramolecular cyclisation or cycloaddition type. On the other hand, there is no document that either describes or suggests for those compounds an *in vivo* activity as activators of the central histaminergic systems, a novel property of the compounds claimed by the Applicant.

More especially, the present invention relates to the compounds of formula (I) :



(I)

wherein :

- **m** and **n**, which may be identical or different, each represent an integer of from 0 to 2 inclusive, with the sum of the two integers being from 2 to 3 inclusive,

- **p** represents 1 or 2,

- **Alk** represents an alkylene, alkenylene or alkynylene chain,

- **X** represents an oxygen atom, a sulphur atom or an –N(R)– group wherein R represents a hydrogen atom or an alkyl group,

- **W** represents a group selected from cyano (when X represents an oxygen atom or an NR' group), $-N(R_1)-Z_1-R_2$ and $-Z_2-NR_1R_2$,
  wherein :
  - R' represents a hydrogen atom or an alkyl group,
  - Z_1 represents $-C(O)-$, $-C(S)-$, $-C(NR_4)-$, $-C(O)-N(R_3)-$, $-C(S)-N(R_3)-$, $-C(NR_4)-N(R_3)-$, $-C(O)-O-$, $-C(S)-O-$ or $-S(O)_r-$, in which r = 1 or 2,
  - Z_2 represents $-C(O)-$, $-C(S)-$, $-C(NR_4)$, $-S(O)_r-$,
  - R_1, R_2, R_3 and R_4, which may be identical or different, each represent a hydrogen atom, an alkyl group, optionally substituted cycloalkyl group, optionally substituted heterocycloalkyl group, optionally substituted aryl group or optionally substituted heteroaryl group,
  - or R_1 and R_2 or R_2 and R_3, together with the nitrogen atom carrying them, form an optionally substituted heterocycloalkyl or optionally substituted heteroaryl group,

to their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base,

wherein:

- the term "alkyl" denotes a linear or branched hydrocarbon chain containing from 1 to 6 carbon atoms,
- the term "alkoxy" denotes an alkyl-oxy group in which the linear or branched alkyl chain contains from 1 to 6 carbon atoms,
- the term "perhaloalkyl" denotes a linear or branched carbon chain containing from 1 to 3 carbon atoms and from 1 to 7 halogen atoms,
- the term "alkylene" denotes a linear or branched bivalent radical containing from 1 to 6 carbon atoms,

- the term "alkenylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 double bonds,
- the term "alkynylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 triple bonds,
- the term "aryl" denotes a phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl or tetrahydronaphthyl group,
- the term "heteroaryl" denotes a monocyclic or bicyclic group in which one of the rings is aromatic, the group containing from 5 to 11 ring members and 1 or 3 hetero atoms selected from nitrogen, oxygen and sulphur,
- the term "cycloalkyl" denotes a hydrocarbon monocycle or bicycle containing from 3 to 11 carbon atoms and optionally unsaturated by 1 or 2 unsaturated bonds,
- the term "heterocycloalkyl" denotes a mono- or bi-cyclic group, saturated or unsaturated by 1 or 2 unsaturated bonds, the group containing from 4 to 11 ring members and having from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,

the expression "optionally substituted" applied to the terms cycloalkyl, aryl, heteroaryl and heterocycloalkyl denotes that those groups may be substituted by from 1 to 3 identical or different substituents selected from alkyl, alkoxy, halogen, hydroxy, perhaloalkyl, nitro, amino (unsubstituted or substituted by one or two alkyl groups), acyl, aminocarbonyl (optionally substituted on the nitrogen atom by one or two alkyl groups), acylamino (optionally substituted on the nitrogen atom by an alkyl group), alkoxycarbonyl, formyl, carboxy, sulpho and cyano, it being understood that the aryl or heteroaryl groups may in addition be substituted by one or two oxo groups on the non-aromatic moiety and that the cycloalkyl or heterocycloalkyl groups may be substituted likewise by one or two oxo groups.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid, etc..

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine etc..

Preferred aryl groups are the phenyl group.

An advantageous embodiment of the invention relates to compounds wherein n and m represent 1.

Other preferred compounds of the invention are those wherein p is 1.

An especially advantageous embodiment of the invention relates to compounds of formula (I) wherein X represents an oxygen atom or a sulphur atom (more advantageously an oxygen atom).

Another especially advantageous embodiment of the invention relates to compounds of formula (I) wherein X represents an –N(R)– group (more advantageously NH).

Advantageously, the compounds of formula (I) are those wherein W :

- represents a $-C(O)-NR_1R_2$ group in which R_1 and R_2, independently, each represent an alkyl group or a hydrogen atom, or R_1 and R_2, together with the nitrogen atom carrying them, form a group selected from pyrrolyl, piperazinyl, piperidinyl, azepanyl, morpholino, thiomorpholino and octahydrocyclopentapyrrolyl,
- represents a $-N(R_1)-C(O)-R_2$ group in which R_1 and R_2, independently, each represent a hydrogen atom or an alkyl group.

More advantageously, W is located in the 4-position of the phenyl group to which it is bonded

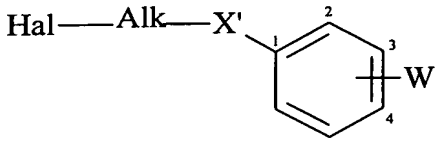
Especially advantageous compounds include compounds of the invention wherein Alk represents an alkylene chain (more especially $-(CH_2)_q-$). More advantageously, the compounds of the invention contain a $-(CH_2)_q-$ chain wherein q=3.

An especially advantageous embodiment of the invention relates to compounds of formula (I) wherein n, m and p are 1, Alk represents a propylene group, W represents a

-C(O)–NR_1R_2 group in which R_1 and R_2, independently, each represent an alkyl group or a hydrogen atom, and W is located in the 4-position of the phenyl group to which it is bonded.

Among the preferred compounds of the invention there may be mentioned, more especially, 4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)benzonitrile and 4-[(3-hexahydrocyclopenta[*c*]-pyrrol-2(1*H*)-ylpropoxy)benzamide.

The invention relates also to a process for the preparation of compounds of formula (I), which is characterised in that there is used as starting material a compound of formula (II) :

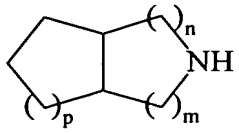


(II)

wherein :

Alk is as defined for formula (I), Hal represents a halogen atom, X' represents an oxygen atom, a sulphur atom or an –N(p)– group, in which (p) represents a hydrogen atom, a conventional protecting group for the nitrogen atom, or an alkyl group, and W is as defined for formula (I),

which compound of formula (II), after deprotection where appropriate, is condensed in basic medium with a bicycle of formula (III) :



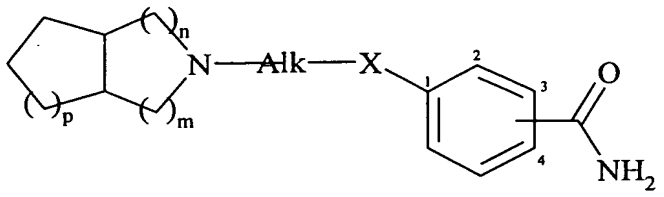
(III)

wherein :

n, m and p are as defined for formula (I), to yield a compound of formula (I),

- which compound of formula (I), when W represents a cyano group, is reacted with sodium hydroxide or potassium hydroxide

to yield a compound of formula (I/b) :



(I/b),

a particular case of the compounds of formula (I) wherein Alk, n, m, p and X are as defined for formula (I),

which compounds of formula (I),

- may, if necessary, be purified according to a conventional purification technique,
- are separated, where appropriate, into stereoisomers according to a conventional separation technique,
- are converted, if desired, into addition salts with a pharmaceutically acceptable acid or base,

it being understood that:

- at any moment considered appropriate during the course of the process described above, the group or groups carbonyl, thiocarbonyl, amino, alkylamino of the starting reagent (II) can be protected and then, after condensation, deprotected, as required by the synthesis,
- the reagents (II) and (III) are prepared according to known procedures described in the literature.

The present invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those which are suitable for oral, parenteral, nasal or transdermal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, etc..

The useful dosage varies in accordance with the age and weight of the patient, the nature and the severity of the disorder, and also the administration route, which may be oral,

nasal, rectal or parenteral. Generally, the unit dosage ranges from 0.05 to 500 mg for a treatment of from 1 to 3 administrations per 24 hours.

The following Examples illustrate the invention and do not limit it in any way. The structures of the described compounds were confirmed by customary spectroscopic and spectrometric techniques.

The starting materials used are known products or products prepared according to known procedures.

PREPARATION 1 : *N*-(4-Chlorobutyl)-*N*-(4-cyanophenyl)acetamide

9 g (54.1 mmol) of *N*-(4-cyanophenyl)acetamide are dissolved in 100 ml of THF. The mixture is cooled to 0°C before the dropwise addition of 51 ml of a 1.6 N solution in hexane of *n*BuLi (1.5 eq.). The solution is left for one hour to return to ambient temperature and is then cooled to 0°C before the dropwise addition of 9.9 ml of 1-chloro-4-iodobutane (81 mmol). The reaction mixture is stirred at ambient temperature for 18 h and then hydrolysed with a saturated aqueous solution of ammonium chloride (100 ml) and extracted with ethyl acetate. The organic phases are combined, dried over magnesium sulphate and concentrated. Purification by chromatography on silica (eluant : petroleum ether/ethyl acetate : 1/1) yields a yellow oil containing the expected product.

PREPARATION 2 : *N*-(3-Chloropropyl)-*N*-(4-cyanophenyl)acetamide

The experimental procedure is identical to that of Preparation 1, with the replacement of 1-chloro-4-iodobutane with 1-chloro-3-iodopropane.

PREPARATION 3 : *N*-(2-Chloroethyl)-*N*-(4-cyanophenyl)acetamide

The experimental procedure is identical to that of Preparation 1, with the replacement of 1-chloro-4-iodobutane with 1-chloro-2-iodoethane.

EXAMPLE 1 : 4-(3-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)benzonitrile oxalate

Step 1 : 4-(3-Chloropropoxy)benzonitrile

A mixture of 0.47 g (0.004 mol) of 4-hydroxybenzonitrile, 0.63 g (0.004 mol) of 1-bromo-3-chloropropane and 1.95 g (0.006 mol) of caesium carbonate in 10 ml of acetonitrile is heated at reflux for 5 hours.

Step 2 : 4-(3-Hexahydrocyclopenta[c]pyrrol-2(1H)-ylpropoxy)benzonitrile oxalate

There are added to the reaction mixture of Step 1, at ambient temperature, 0.44 g (0.004 mol) of octahydrocyclopenta[*c*]pyrrole and 0.30 g (0.002 mol) of sodium iodide and heating at reflux is resumed for 16 hours. The precipitate is filtered off and rinsed with acetonitrile. The filtrate is concentrated to dryness. The residue is taken up in dichloromethane. The resulting solution is extracted with sodium hydroxide solution, then with water, dried over magnesium sulphate and concentrated to dryness. The residue is purified by preparative chromatography technique on Lichroprep RP-18 phase. The title product is recrystallised from ethanol in oxalate form.

ESI$^+$: [M+H] 271.1810 (theory : 271.1810)

EXAMPLE 2 : 4-(2-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylethoxy)benzonitrile oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 1-bromo-3-chloropropane in Step 1 with 1-bromo-2-chloroethane.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*62.42*	*6.40*	*8.09*
Found :	*62.09*	*6.38*	*8.09*

EXAMPLE 3 : 4-(4-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylbutoxy)benzonitrile oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 1-bromo-3-chloropropane in Step 1 with 1-bromo-2-chlorobutane.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*63.28*	*6.89*	*7.31*
Found :	*62.14*	*6.78*	*6.91*

EXAMPLE 4 : *N*-[4-(3-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)-phenyl]acetamide oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with *N*-(4-hydroxyphenyl)acetamide.

^{1}H NMR (DMSO D_6) : δ (ppm) : 1.40-1.80 (m,6*H*) ; 2.00 (s,3*H*) ; 2.10 (quint,2*H*) ; 2.80 (m,4*H*) ; 3.25 (t,2*H*) ; 3.60 (m,2*H*) ; 4.00 (t,2*H*) ; 6.90 (d,2*H*) ; 7.50 (d,2*H*) ; 9.80 (s,1*H*).

EXAMPLE 5 : *N*-[3-(3-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)-phenyl]acetamide oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with *N*-(3-hydroxyphenyl)acetamide.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*61.21*	*7.19*	*7.14*
Found :	*61.06*	*7.28*	*7.06*

EXAMPLE 6 : *N*-Ethyl-4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)-benzamide oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with *N*-ethyl-4-hydroxybenzamide.

EXAMPLE 7 : *N*-Cyclopentyl-4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)-benzamide oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with *N*-cyclopentyl-4-hydroxybenzamide.

EXAMPLE 8 : *N*-Cyclopentyl-*N*-ethyl-4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)benzamide oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with *N*-cyclopentyl-*N*-ethyl-4-hydroxybenzamide.

EXAMPLE 9 : *N,N*-Diethyl-4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)-benzamide oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with *N,N*-diethyl-4-hydroxybenzamide.

EXAMPLE 10 : *N,N*-Dicyclopropyl-4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)benzamide oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with *N,N*-dicyclopropyl-4-hydroxybenzamide.

EXAMPLE 11 : 2-{3-[4-(1-Azepanylcarbonyl)phenoxy]propyl}octahydrocyclopenta-[*c*]pyrrole oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with 4-(1-azepanylcarbonyl)phenol.

EXAMPLE 12 : 2-{3-[4-(Thiomorpholinocarbonyl)phenoxy]propyl}octahydrocyclopenta[*c*]pyrrole oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with 4-(thiomorpholinocarbonyl)phenol.

EXAMPLE 13 : 2-{3-[4-(Morpholinocarbonyl)phenoxy]propyl}octahydrocyclopenta[*c*]pyrrole oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with 4-(morpholinocarbonyl)phenol.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*61.59*	*7.19*	*6.25*
Found :	*61.50*	*7.21*	*6.30*

EXAMPLE 14 : 2-{3-[4-(1-Piperazinylcarbonyl)phenoxy]propyl}octahydrocyclopenta[*c*]pyrrole oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with 4-(1-piperazinylcarbonyl)phenol.

EXAMPLE 15 : 2-[4-(3-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)benzoyl]-isoindoline oxalate

The experimental procedure is identical to that of Example 1, with the replacement of

4-hydroxybenzonitrile in Step 1 with 4-(1,3-dihydro-2*H*-isoindol-2-ylcarbonyl)phenol.

EXAMPLE 16 : 5-Bromo-2-[4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)-benzoyl]isoindoline oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with 4-[(5-bromo-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]-phenol.

EXAMPLE 17 : 2-{3-[4-(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylcarbonyl)phenoxy]-propyl}octahydrocyclopenta[*c*]pyrrole oxalate

The experimental procedure is identical to that of Example 1, with the replacement of 4-hydroxybenzonitrile in Step 1 with 4-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylcarbonyl)-phenol.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*62.65*	*7.21*	*5.41*
Found :	*63.14*	*7.30*	*5.47*

EXAMPLE 18 : 4-[(4-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylbutyl)amino]-benzonitrile oxalate

Step 1 : *N*-(4-Cyanophenyl)-*N*-(4-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylbutyl)-acetamide

2 g (8 mmol) of the chlorine compound synthesised in Preparation 1 are dissolved in 65 ml of ethanol with 1.5 g of octahydrocyclopenta[c]pyrrole (2 eq.) and 12 mg of NaI (0.01 eq.). The mixture is heated at reflux for 18 hours before being evaporated to dryness *in vacuo*. The residue is taken up in ethyl acetate and then washed with N sodium hydroxide solution. The organic phase is dried over magnesium sulphate, concentrated and purified by column chromatography on silica (eluant : dichloromethane/ethanol : 9/1) to yield 1.4 g

of the expected product.

Step 2 : 4-[(4-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylbutyl)amino]benzonitrile oxalate

133 mg (1.5 eq.) of sodium ethanolate are added to a solution of the compound prepared in the above Step (423 mg) in 2.6 ml of ethanol. The mixture is heated at reflux for 5 hours and then concentrated *in vacuo*. The residue is taken up in dichloromethane, washed with water and then dried over magnesium sulphate before evaporation of the solvent. Purification by column chromatography (eluant : dichloromethane/ethanol/ammonium hydroxide : 10/0.5/0.25) allows 330 mg of product to be obtained. 260 mg of that compound are dissolved in ethanol and then the addition of 2.5 equivalents of oxalic acid in solution in ethanol results in precipitation of the salt.

ESI$^+$: *[M+H] 284.2085 (theory : 284.2127)*

EXAMPLE 19 : 4-[(3-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropyl)amino]benzonitrile oxalate

The experimental procedure is identical to that of Example 18, with the replacement of the reagent of Preparation 1 with that of Preparation 2.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*63.49*	*7.01*	*11.69*
Found :	*63.22*	*7.04*	*11.47*

EXAMPLE 20 : 4-[(2-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylethyl)amino]benzonitrile oxalate

The experimental procedure is identical to that of Example 18, with the replacement of the reagent of Preparation 1 with that of Preparation 3.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*60.81*	*6.49*	*11.56*
Found :	*60.60*	*6.00*	*11.30*

EXAMPLE 21 : 4-[(4-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylbutyl)amino]-benzamide oxalate

436 mg of the compound of Example 18 are dissolved in 4 ml of ethanol. 86 mg of potassium hydroxide (1 eq.) are dissolved in 1.5 ml of water before being added to the alcohol solution. The mixture is heated at reflux for 1.5 hours and then evaporated to dryness. The residue is taken up in dichloromethane. The resulting solution is washed with water, dried over magnesium sulphate and then concentrated *in vacuo*. The product is crystallised in oxalate form.

ESI$^+$: [M+H] 302.2212 (theory : 302.2232)

EXAMPLE 22 : 4-(3-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)benzamide oxalate

The experimental procedure is identical to that of Example 21, using the compound of Example 1 as starting material.

Elemental microanalyses :

	C %	*H %*	*N %*
Calculated :	*55.50*	*6.26*	*6.35*
Found :	*54.67*	*6.08*	*6.28*

EXAMPLE 23 : 4-[(3-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropyl)amino]-benzamide oxalate

The experimental procedure is identical to that of Example 21, using the compound of Example 19 as starting material.

EXAMPLE 24 : 4-[(2-Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylethyl)amino]benzamide oxalate

The experimental procedure is identical to that of Example 21, using the compound of Example 20 as starting material.

PHARMACOLOGICAL STUDIES OF THE COMPOUNDS OF THE INVENTION

EXAMPLE A : Cerebral doses of N^t-methylhistamine in the NMRI mouse

The aim of this study, carried out according to the method of Taylor *et al.* (*Biochem. Pharm.*, 1992, 44, 1261-1267), is to evaluate the *ex vivo* activity of the compounds of the present invention as type H3 central histaminergic receptor antagonists. That activity is revealed by measuring central levels of N^t-methylhistamine, the principal metabolite of histamine, after oral administration of the compounds being studied. An increase in the cerebral concentrations of N^t-methylhistamine signifies an increase in histamine turnover by blockade of the type H3 central histaminergic receptors.

NMRI mice (18-20g) are treated *via* oral administration with the compounds of the present invention or with their carrier (20 ml/kg). Two hours after the pharmacological treatment, the animals are sacrificed, the brains are removed, frozen in liquid nitrogen, weighed and homogenised in 0.1N $HClO_4$ at 4°C. The homogenates are centrifuged (15000 g, 17 min, 4°C). The supernatants are recovered and divided into aliquots. The aliquots are frozen in liquid nitrogen and stored at -80°C until their analysis.

Determination of the cerebral levels of N^t-methylhistamine is effected by capillary electrophoresis coupled with detection by laser-induced fluorescence (*J. Chromatogr. A.*, 1996, 755, 99-115). The tissue levels of N^t-methylhistamine are expressed in ng/g of fresh brain. Comparison between the cerebral levels of N^t-methylhistamine of the animals treated with the carrier (control) and the animals treated with the compounds of the present invention (n=5/group) is effected by single factor variance analysis followed, if necessary, by a supplementary analysis (Dunnett's test).

The results show that, at doses of from 3 to 10 mg/kg p.o., the compounds of the present invention are capable of increasing the endogenous cerebral concentrations of N^t-methylhistamine by more than 50 %. By way of example, at doses of 3 mg/kg p.o., the compounds of Examples 4 and 22 increase the endogenous cerebral concentrations of N^t-methylhistamine by 52 % and 33 % respectively, and, at a dose of 10 mg/kg p.o., the compound of Example 22 increases the endogenous cerebral concentrations of N^t-methylhistamine by 85 %. These results demonstrate that the compounds of the present invention are potent activators of the central histaminergic systems and are active *via* the oral route with a duration of action of at least several hours.

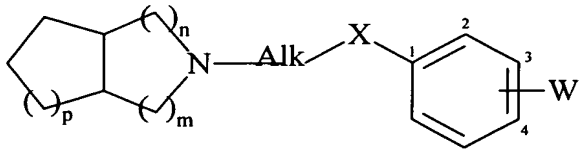
EXAMPLE B : Pharmaceutical compositions

Formulation for the preparation of 1000 tablets each containing a dose of 100 mg :

compound of Example 22	100 g
hydroxypropyl cellulose	20 g
polyvinylpyrrolidone	20 g
wheat starch	150 g
lactose	900 g
magnesium stearate	30 g

CLAIMS

1- Compounds of formula (I) :



(I)

wherein :

- **m** and **n**, which may be identical or different, each represent an integer of from 0 to 2 inclusive, with the sum of the two integers being from 2 to 3 inclusive,
- **p** represents 1 or 2,
- **Alk** represents an alkylene, alkenylene or alkynylene chain,
- **X** represents an oxygen atom, a sulphur atom or an –N(R)– group wherein R represents a hydrogen atom or an alkyl group,
- **W** represents a group selected from cyano (when X represents an oxygen atom or an NR' group), $-N(R_1)-Z_1-R_2$ and $-Z_2-NR_1R_2$,

  wherein :
  - R' represents a hydrogen atom or an alkyl group,
  - Z_1 represents –C(O)–, –C(S)–, $-C(NR_4)-$, $-C(O)-N(R_3)-$, $-C(S)-N(R_3)-$, $-C(NR_4)-N(R_3)-$, –C(O)–O–, –C(S)–O– or $-S(O)_r-$, in which r = 1 or 2,
  - Z_2 represents –C(O)–, –C(S)–, $-C(NR_4)$, $-S(O)_r-$,
  - R_1, R_2, R_3 and R_4, which may be identical or different, each represent a hydrogen atom, an alkyl group, optionally substituted cycloalkyl group, optionally substituted heterocycloalkyl group, optionally substituted aryl group or optionally substituted heteroaryl group,
  - or R_1 and R_2 or R_2 and R_3, together with the nitrogen atom carrying them, form an

optionally substituted heterocycloalkyl or optionally substituted heteroaryl group,

their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base,

wherein:

- the term "alkyl" denotes a linear or branched hydrocarbon chain containing from 1 to 6 carbon atoms,
- the term "alkoxy" denotes an alkyl-oxy group in which the linear or branched alkyl chain contains from 1 to 6 carbon atoms,
- the term "perhaloalkyl" denotes a linear or branched carbon chain containing from 1 to 3 carbon atoms and from 1 to 7 halogen atoms,
- the term "alkylene" denotes a linear or branched bivalent radical containing from 1 to 6 carbon atoms,
- the term "alkenylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 double bonds,
- the term "alkynylene" denotes a linear or branched bivalent radical containing from 2 to 6 carbon atoms and from 1 to 3 triple bonds,
- the term "aryl" denotes a phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl or tetrahydronaphthyl group,
- the term "heteroaryl" denotes a monocyclic or bicyclic group in which one of the rings is aromatic, containing from 5 to 11 ring members and 1 or 3 hetero atoms selected from nitrogen, oxygen and sulphur,
- the term "cycloalkyl" denotes a hydrocarbon monocycle or bicycle containing from 3 to 11 carbon atoms and optionally unsaturated by 1 or 2 unsaturated bonds,
- the term "heterocycloalkyl" denotes a mono- or bi-cyclic group, saturated or unsaturated by 1 or 2 unsaturated bonds, containing from 4 to 11 ring members and having from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,

the expression "optionally substituted" applied to the terms cycloalkyl, aryl, heteroaryl and heterocycloalkyl denotes that those groups may be substituted by from 1 to 3 identical or different substituents selected from alkyl, alkoxy, halogen, hydroxy, perhaloalkyl, nitro,

amino (unsubstituted or substituted by one or two alkyl groups), acyl, aminocarbonyl (optionally substituted on the nitrogen atom by one or two alkyl groups), acylamino (optionally substituted on the nitrogen atom by an alkyl group), alkoxycarbonyl, formyl, carboxy, sulpho and cyano, it being understood that the aryl or heteroaryl groups may in addition be substituted by one or two oxo groups on the non-aromatic moiety and that the cycloalkyl or heterocycloalkyl groups may be substituted likewise by one or two oxo groups.

2- Compounds of formula (I) according to claim 1, wherein n and m are each 1, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

3- Compounds of formula (I) according to claim 1 or 2, wherein p is 1, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

4- Compounds of formula (I) according to any one of claims 1 to 3, wherein X represents an oxygen atom or a sulphur atom, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

5- Compounds of formula (I) according to any one of claims 1 to 4, wherein X represents an –N(R)– group, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

6- Compounds of formula (I) according to any one of claims 1 to 5, wherein W :

- represents a $-C(O)-NR_1R_2$ group in which R_1 and R_2 represent an alkyl group or a hydrogen atom, or R_1 and R_2, together with the nitrogen atom carrying them, form a group selected from pyrrolyl, piperazinyl, piperidinyl, morpholino, azepanyl, thiomorpholino and octahydrocyclopentapyrrolyl,
- represents a $-N(R_1)-C(O)-R_2$ group in which R_1 and R_2, independently, each represent a hydrogen atom or an alkyl group,

their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically

acceptable acid or base.

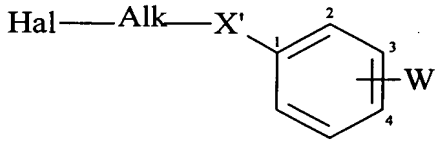
7- Compounds of formula (I) according to any one of claims 1 to 6, wherein Alk represents an alkylene chain, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

8- Compounds of formula (I) according to any one of claims 1 to 7, wherein n, m and p are 1, Alk represents a propylene group, W represents a -C(O)-NR_1R_2 group in which R_1 and R_2, independently, each represent an alkyl group or a hydrogen atom, and W is located in the 4-position of the phenyl group to which it is bonded, their enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid or base.

9- Compound of formula (I) according to any one of claims 1 to 8, which is 4-(3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropoxy)benzonitrile, its enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid.

10- Compound of formula (I) according to any one of claims 1 to 8, which is 4-(3-hexahydrocyclopenta[*c*]-pyrrol-2(1*H*)-ylpropoxy)benzamide, its enantiomers, diastereoisomers, and also addition salts thereof with a pharmaceutically acceptable acid.

11- Process for the preparation of the compounds of formula (I) according to claim 1, characterised in that there is used as starting material a compound of formula (II) :

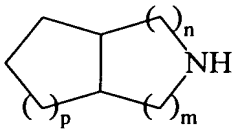


(II)

wherein :

Alk is as defined for formula (I), Hal represents a halogen atom, X' represents an oxygen atom, a sulphur atom or an –N(p)– group, in which (p) represents a hydrogen atom, a conventional protecting group for the nitrogen atom, or an alkyl group, and W is as defined for formula (I),

which compound of formula (II), after deprotection where appropriate, is condensed in basic medium with a bicycle of formula (III) :



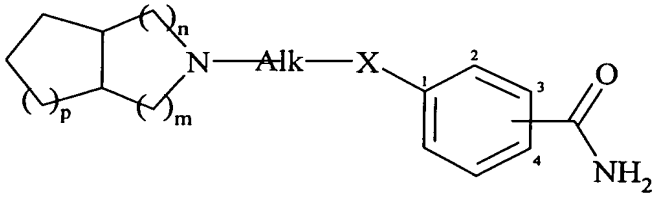
(III)

wherein :

n, m and p are as defined for formula (I), to yield a compound of formula (I),

- which compound of formula (I), when W represents a cyano group, is reacted with sodium hydroxide or potassium hydroxide

to yield a compound of formula (I/b) :



(I/b),

a particular case of the compounds of formula (I) wherein Alk, n, m, p and X are as defined for formula (I),

which compounds of formula (I),

- may, if necessary, be purified according to a conventional purification technique,
- are separated, where appropriate, into stereoisomers according to a conventional separation technique,
- are converted, if desired, into addition salts with a pharmaceutically acceptable acid or base,

it being understood that:

- at any moment considered appropriate during the course of the process described above, the group or groups carbonyl, thiocarbonyl, amino, alkylamino of the starting reagent (II) can be protected and then, after condensation, deprotected, as required by the synthesis,
- the reagents (II) and (III) are prepared according to known procedures described in the literature.

12- Pharmaceutical compositions comprising as active ingredient at least one compound

according to any one of claims 1 to 10, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

13- Pharmaceutical compositions according to claim 12, containing at least one active ingredient according to any one of claims 1 to 10, for use as a medicament in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases, and also in the treatment of mood disorders, convulsive attacks, attention deficit hyperactivity syndrome, obesity and pain.

14- Pharmaceutical compositions according to claim 12, containing at least one active ingredient according to any one of claims 1 to 10, for use as a medicament in the treatment of cognitive deficiencies associated with Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and sub-cortical dementias of vascular or other origins.

15- Use of a pharmaceutical composition according to claim 12, containing at least one active ingredient according to any one of claims 1 to 10, for the manufacture of medicaments for use in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases, and also in the treatment of mood disorders, convulsive attacks, attention deficit hyperactivity syndrome, obesity and pain.

16- Use of the pharmaceutical composition according to claim 12, containing at least one active ingredient according to any one of claims 1 to 10, for the manufacture of medicaments for use in the treatment of cognitive deficiencies associated with Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and sub-cortical dementias of vascular or other origins.

Received on 12/03/04

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PATENT OF INVENTION
UTILITY CERTIFICATE
Intellectual Property Code - Book VI

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Page No. 1 / 2
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Your references for this file *(optional)*	38093
NATIONAL REGISTRATION NO.	0401690

TITLE OF THE INVENTION (maximum 200 characters or spaces)

New azabicyclic compounds, a process for their preparation and pharmaceutical compositions containing them

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20 February 2004

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